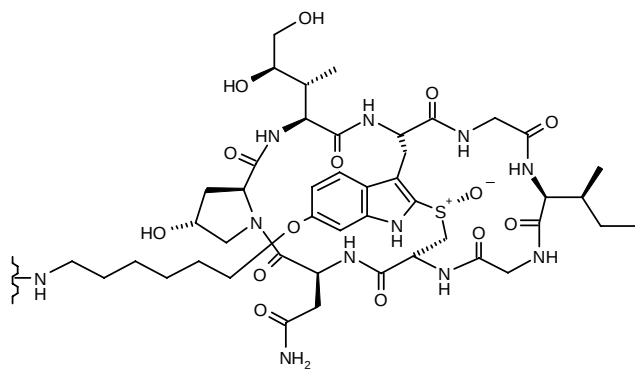


What is claimed is:

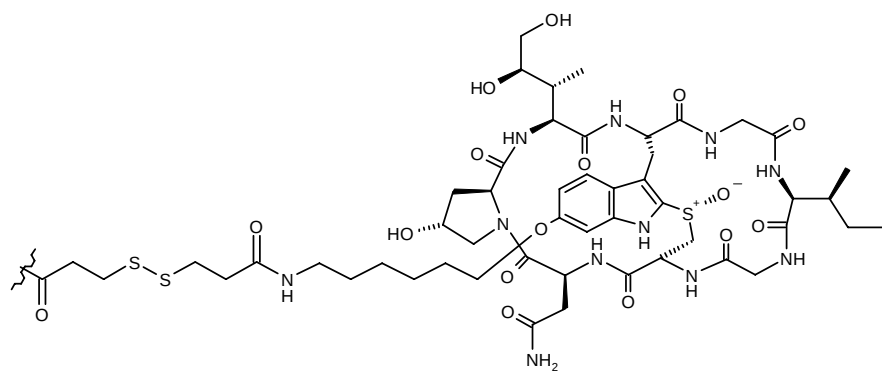
1. Use of a composition for use in the manufacture of a medicament for the treatment of cancer, the composition comprising
 - (a) at least one immune checkpoint inhibitor and
 - (b) at least one conjugate, wherein said conjugate is comprising
 - (i) a target binding moiety,
 - (ii) at least one amatoin, and
 - (iii) optionally at least one linker connecting said target binding moiety with said at least one amatoin;
- ~~2. The composition for use of claim 1, wherein said immune checkpoint inhibitor and/or the target binding moiety of said conjugate is selected from the group consisting of~~
 - (i) an antibody, preferably a monoclonal antibody,
 - (ii) an antigen-binding fragment thereof, preferably a variable domain (Fv), a Fab fragment or an F(ab)₂ fragment,
 - (iii) an antigen-binding derivative thereof, preferably a single-chain Fv (scFv), and
 - (iv) an antibody-like protein.
- ~~23. The Use of the composition for use according to claim 12 in the manufacture of a medicament for the treatment of cancer, wherein said antibody, or antigen-binding fragment thereof or antigen-binding derivative thereof, is a murine, a chimeric, a humanized or a human antibody, or antigen-binding fragment or antigen-binding derivative thereof, respectively.~~
- ~~34. The Use of the composition for use according to any of claims 1 or to 23 in the manufacture of a medicament for the treatment of cancer, wherein said immune checkpoint inhibitor binds to an immune checkpoint receptor selected from the group consisting of PD-1, CTLA-4, LAG-3, TIGIT, TIM-3, VISTA, BTLA, CD96 and CD160, or to a ligand of an immune checkpoint receptor selected from the group consisting of PD-L1, PD-L2, CD80, CD86, Galectin-3, LSECtin, CD112, Ceacam-1, Gal-9, PtdSer, HMGB1, HVEM, CD155.~~

- ~~45.~~ ~~The Use of the composition for use~~ according to any of claims ~~12~~ to ~~34~~ in the manufacture of a medicament for the treatment of cancer, wherein said immune checkpoint inhibitor is an antibody selected from the group consisting of nivolumab, , pidilizumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab and ipilimumab, or an antigen-binding fragment thereof, or an antigen-binding derivative thereof, preferably wherein the antibody is avelumab, pembrolizumab, nivolumab, or ipilimumab or an antigen-binding fragment thereof, or an antigen-binding derivative thereof.
- ~~56.~~ ~~The Use of the composition for use~~ according to any of claims 1 to ~~45~~ in the manufacture of a medicament for the treatment of cancer, wherein the composition is comprising a combination of two or more immune checkpoint inhibitors, preferably wherein the composition is comprising a combination of two immune checkpoint inhibitors.
- ~~67.~~ ~~The Use of the composition for use~~ according to any of claims 1 to ~~56~~ in the manufacture of a medicament for the treatment of cancer, wherein the target binding moiety of said conjugate binds to a target molecule on the cell surface of cancer cells selected from the group comprising PSMA, CD19, CD37, CD269, sialyl Lewis^a, HER-2/neu, epithelial cell adhesion molecule (EpCAM).
- ~~78.~~ ~~The Use of the composition for use~~ according to any of claims 1 to ~~67~~ in the manufacture of a medicament for the treatment of cancer, wherein the target binding moiety of said conjugate is an antibody having an Fc region comprising at least one mutation selected from the group consisting of D265C, D265A, A118C, L234A, and/or L235A (according to the EU numbering system).
- ~~89.~~ ~~The Use of the composition for use~~ according to claim ~~78~~ in the manufacture of a medicament for the treatment of cancer, wherein said antibody is ~~comprising~~comprises an Fc region carrying a D265C mutation and wherein said linker, if present, or said amatoxin is connected to said antibody via the D265C residue of said antibody, preferably via a thioether - linkage.

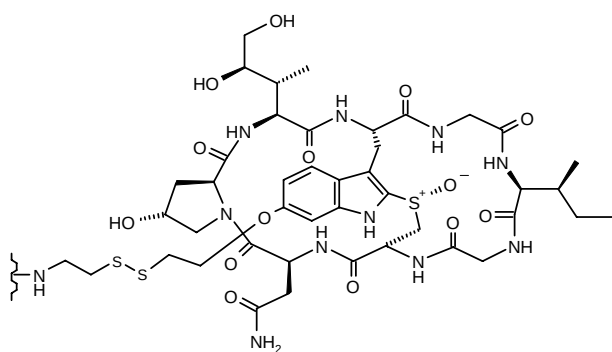
- ~~910.~~ The Use of the composition for use according to any of claims 1 to ~~89~~ in the manufacture of a medicament for the treatment of cancer, wherein the amatoxin of said conjugate is selected from α -amanitin, β -amanitin, γ -amanitin, ϵ -amanitin, amanin, amaninamide, amanullin, amanullinic acid, or from salts or analogues thereof.
- ~~1011.~~ The Use of the composition for use according to any of claims 1 to ~~89~~ in the manufacture of a medicament for the treatment of cancer, wherein the linker of said conjugate, if present, is a stable or a cleavable linker, and wherein said cleavable linker is selected from the group consisting of an enzymatically cleavable linker, preferably a protease-cleavable linker, and a chemically cleavable linker, preferably a linker comprising a disulfide bridge.
- ~~1112.~~ The Use of the composition for use according to any of claims 1 to ~~1011~~ in the manufacture of a medicament for the treatment of cancer, wherein the linker of said conjugate, if present, or said target binding moiety is connected to said amatoxin via (i) the γ C-atom of amatoxin amino acid 1, or (ii) the δ C-atom of amatoxin amino acid 3, or (iii) the 6'-C-atom of amatoxin amino acid 4.
- ~~1213.~~ The Use of the composition for use according to any of claims 1 to ~~1112~~ in the manufacture of a medicament for the treatment of cancer, wherein said conjugate comprises any of the following compounds of formulas (I) to (XII), respectively, as linker-amatoxin moieties:



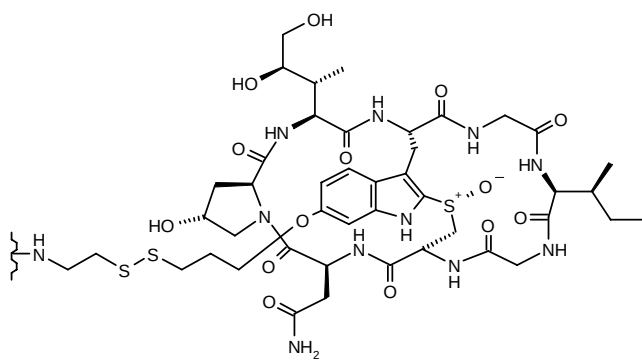
(I)



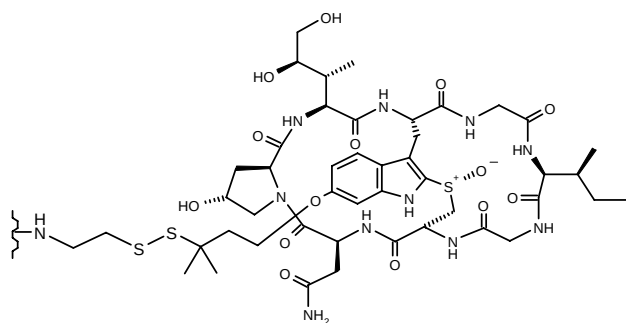
(II)



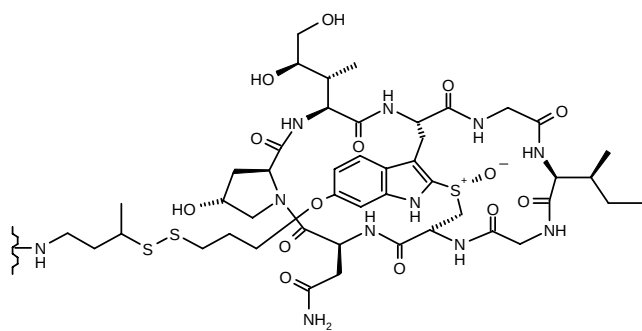
(III)



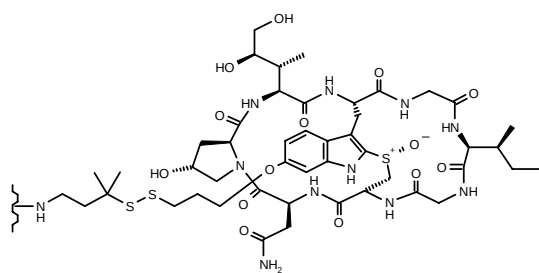
(IV)



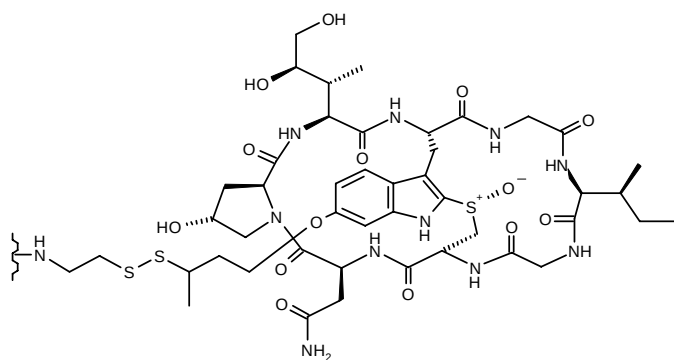
(V)



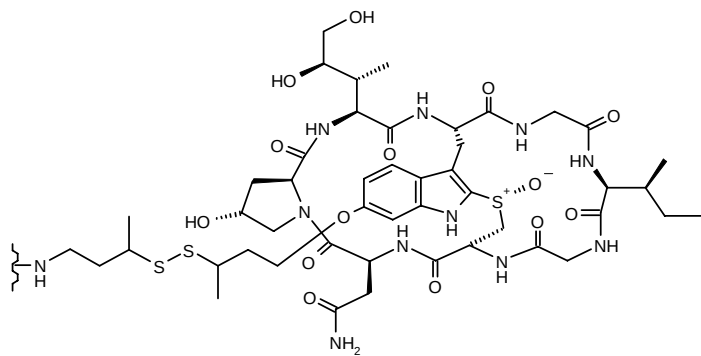
(VI)



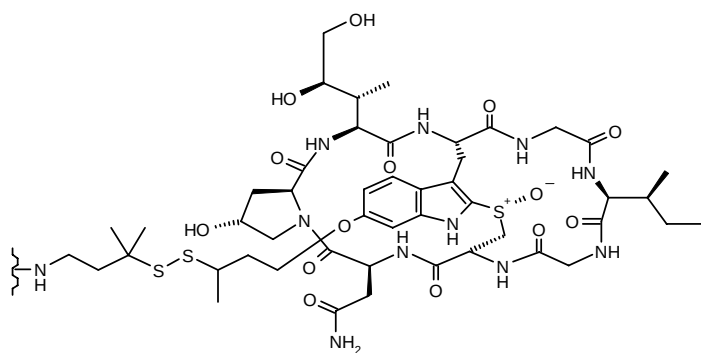
(VII)



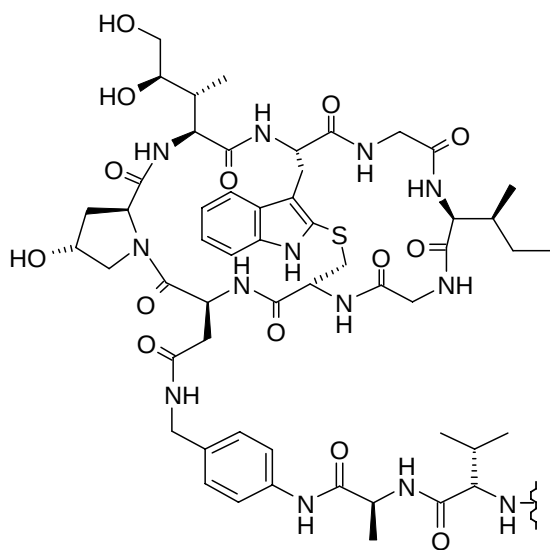
(VIII)



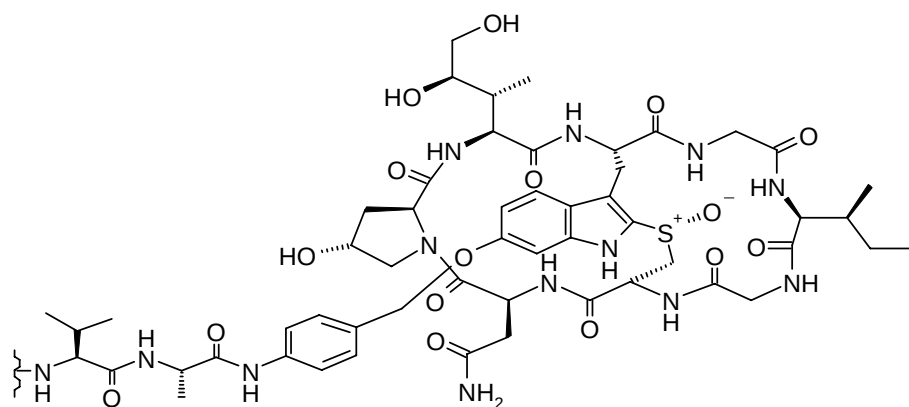
(IX)



(X)

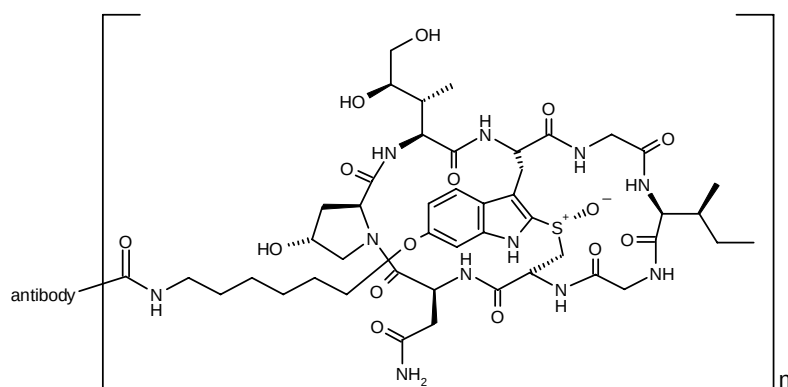


(XI)

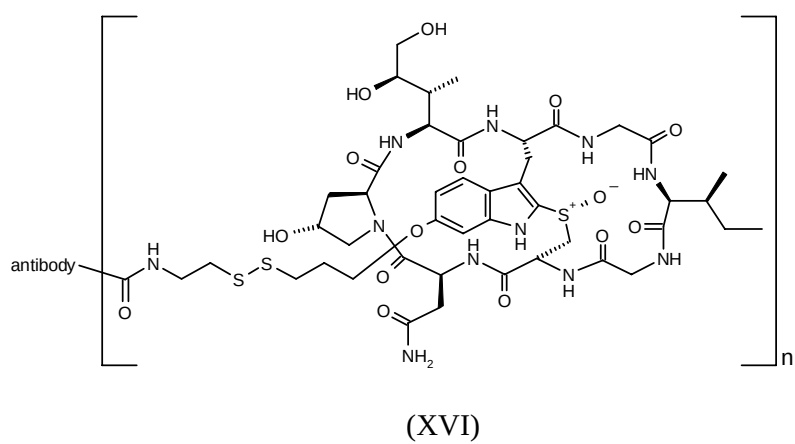
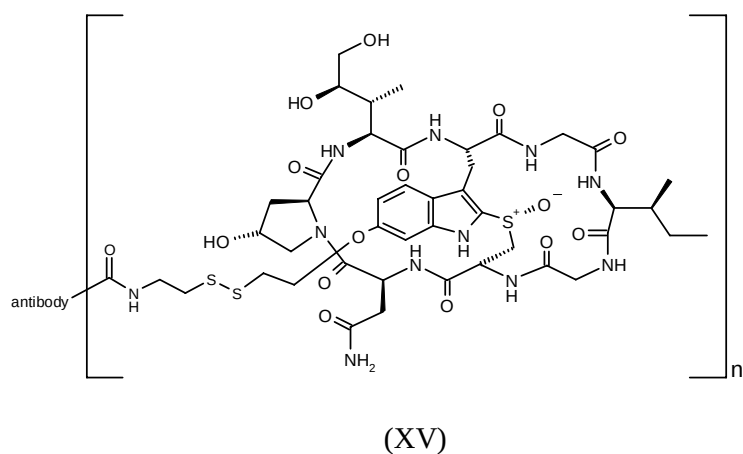
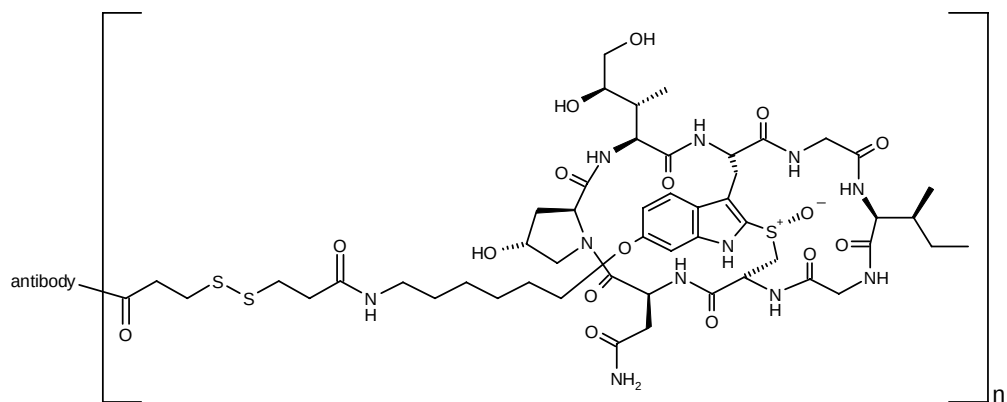


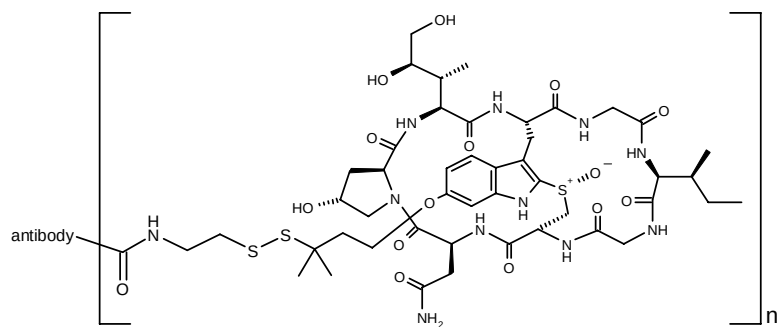
(XII)

1314. The Use of the composition for use according to any of claims 1 to 1142 in the manufacture of a medicament for the treatment of cancer, wherein said conjugate is a compound according to any one of formula XIII to XXII:

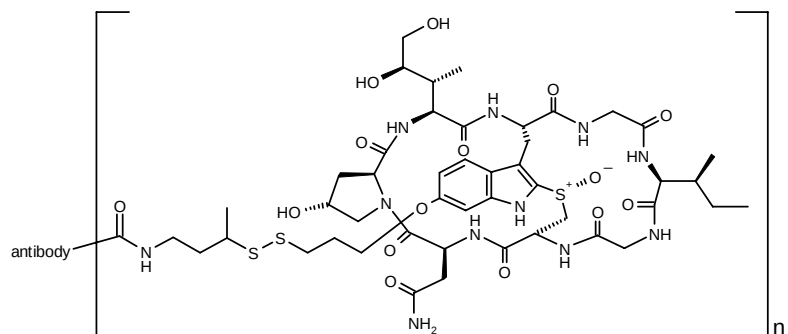


(XIII)

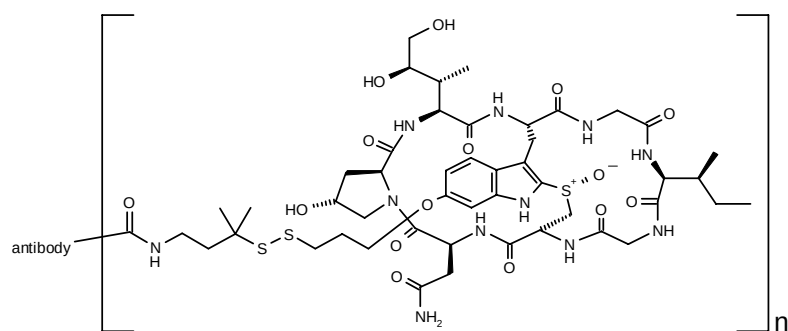




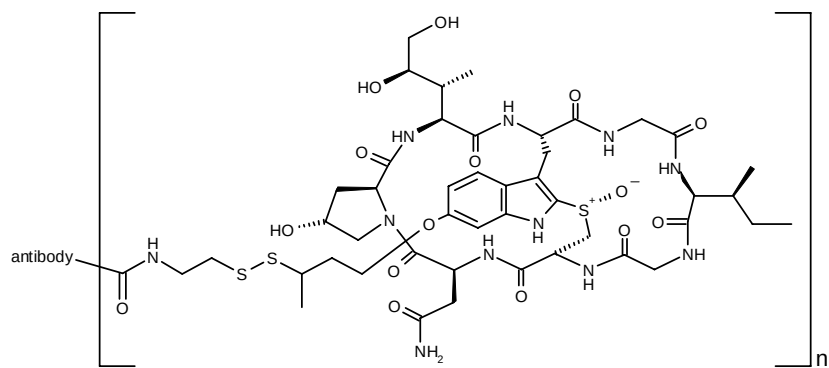
(XVII)



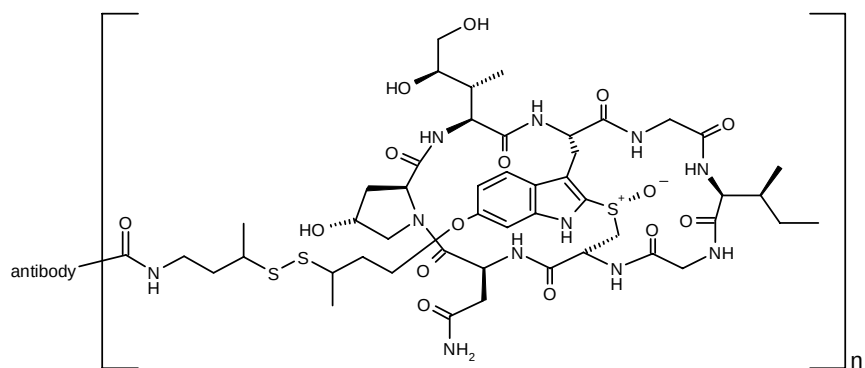
(XVIII)



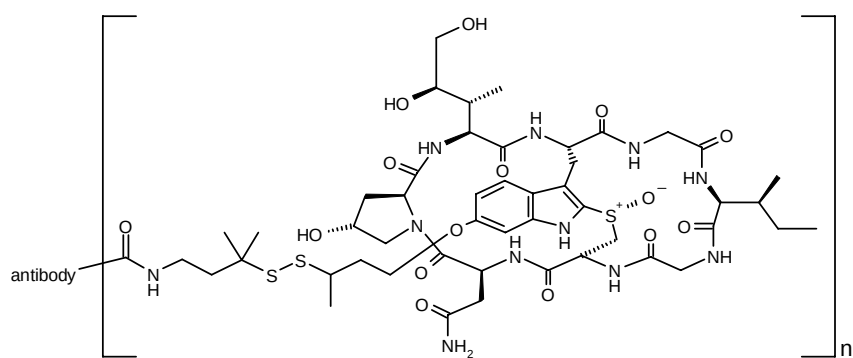
(XIX)



(XX)



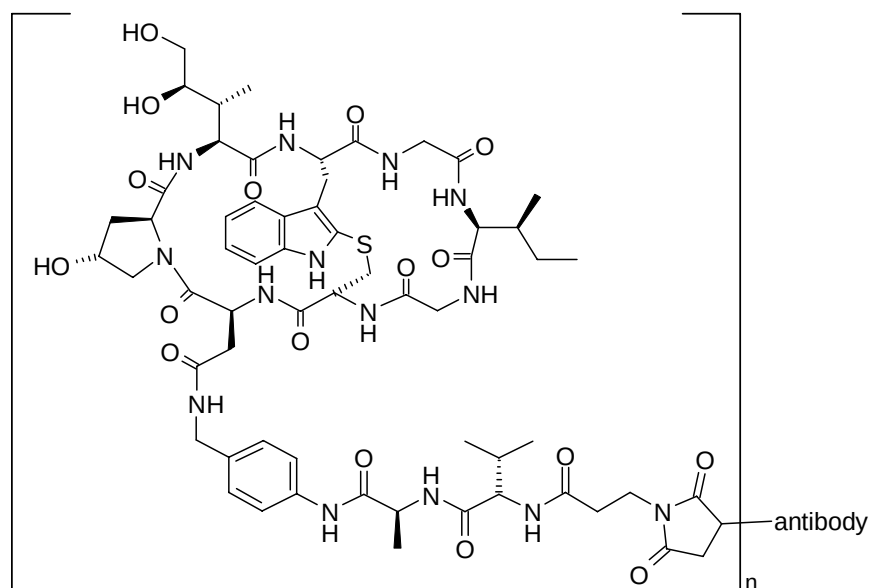
(XXI)



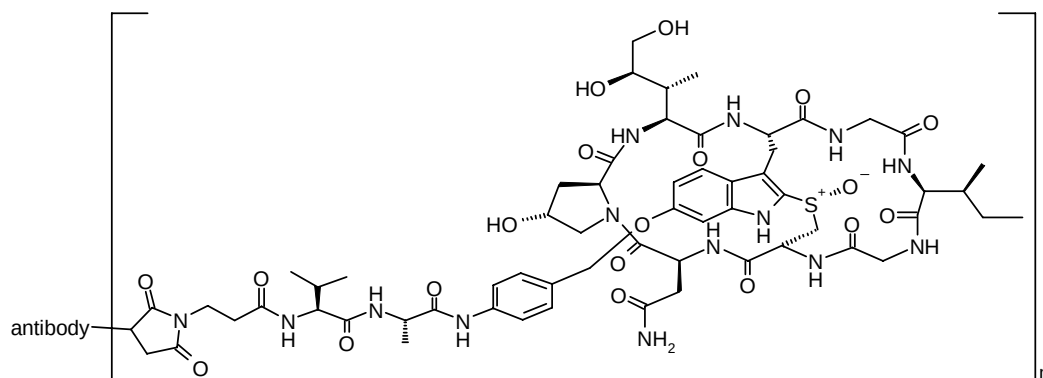
(XXII)

wherein said amatoxin linker moieties are coupled to ϵ -amino groups of naturally occurring lysine residues of said antibody, and wherein n is preferably from 1 to 8.

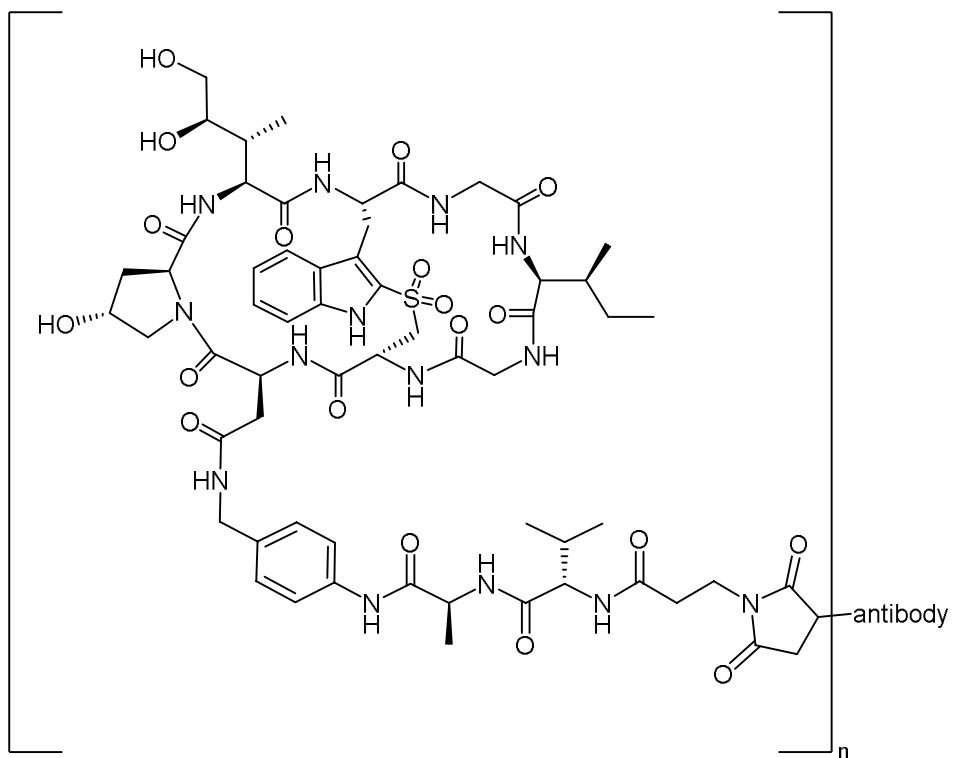
1415. The Use of the composition for use according to any of claims 1 to 1142 in the manufacture of a medicament for the treatment of cancer, wherein said conjugate is a compound according to any one of formula XXIII, XXIV, XVIIIb, XVb, XVIb, XVIIb, XVIIIb, XIXb, XXb, XXIIb :



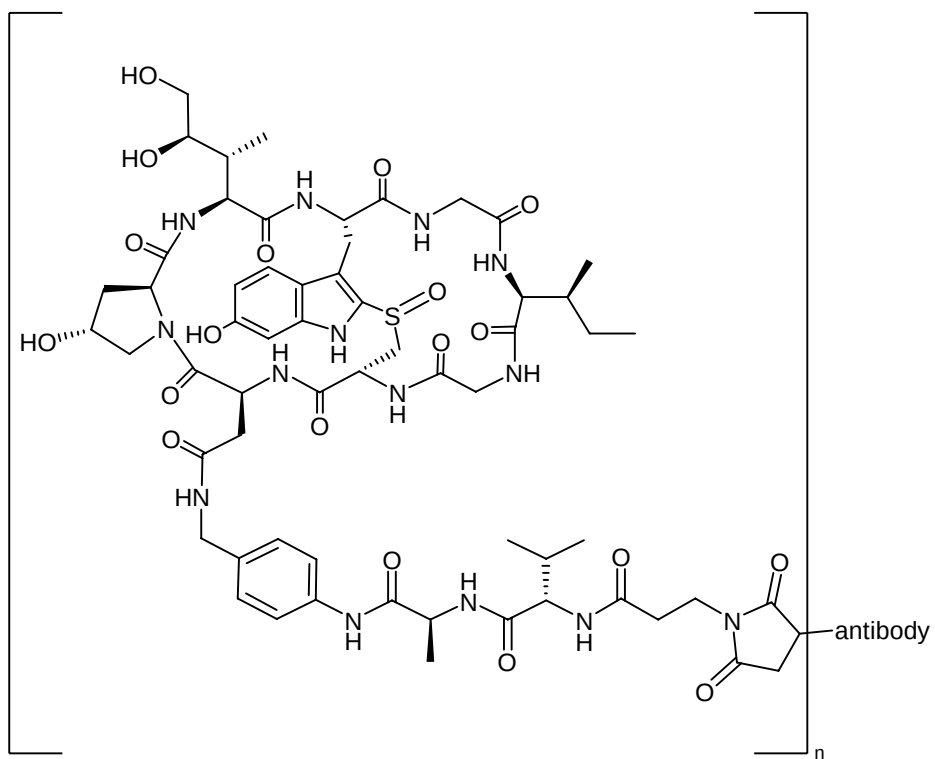
(XXIII)



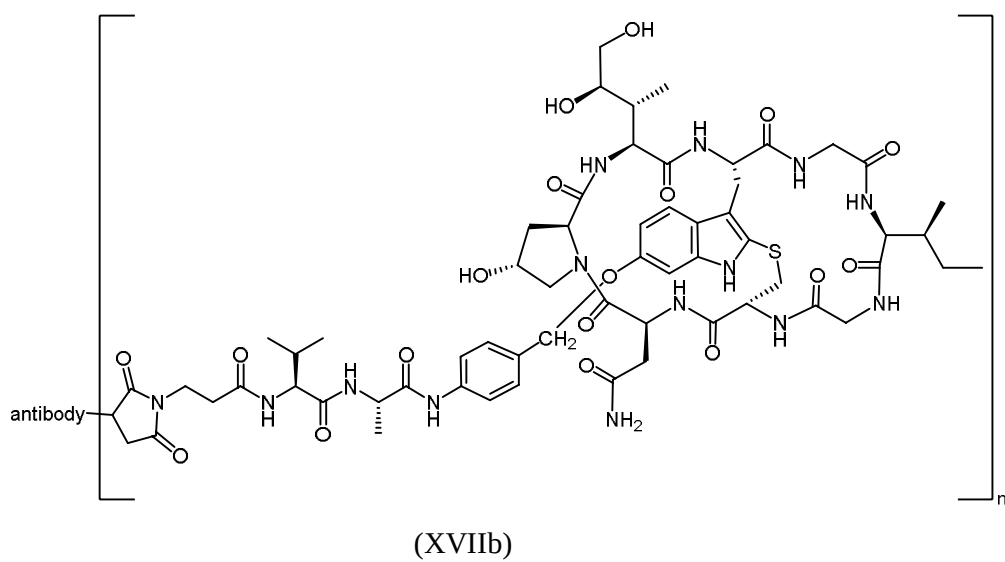
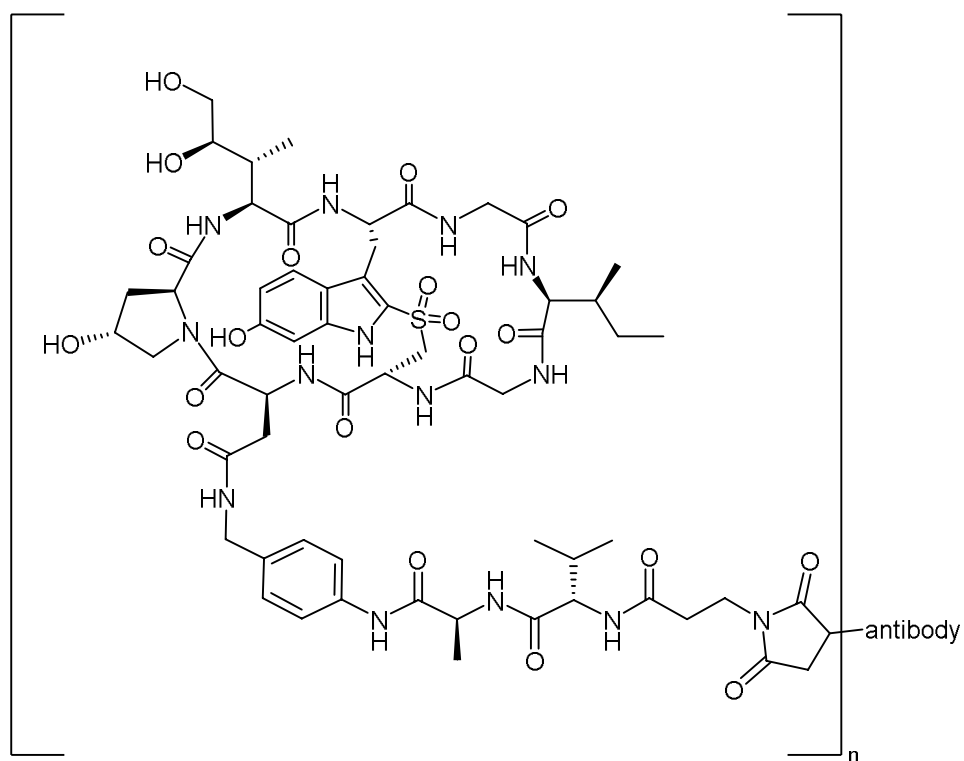
(XXIV)

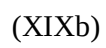


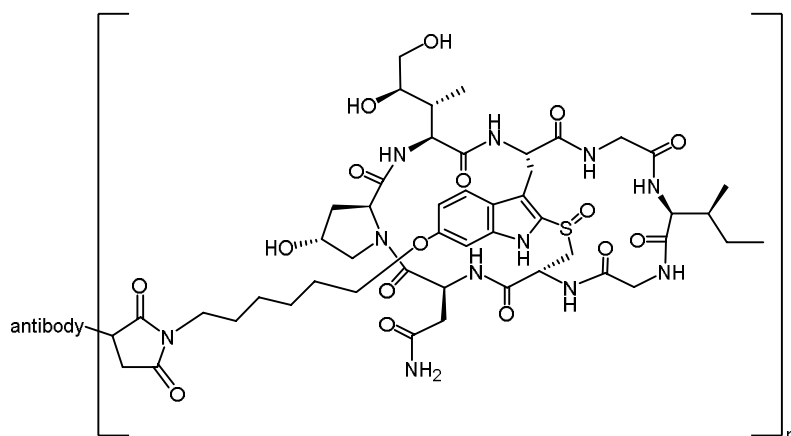
(XIIIb)



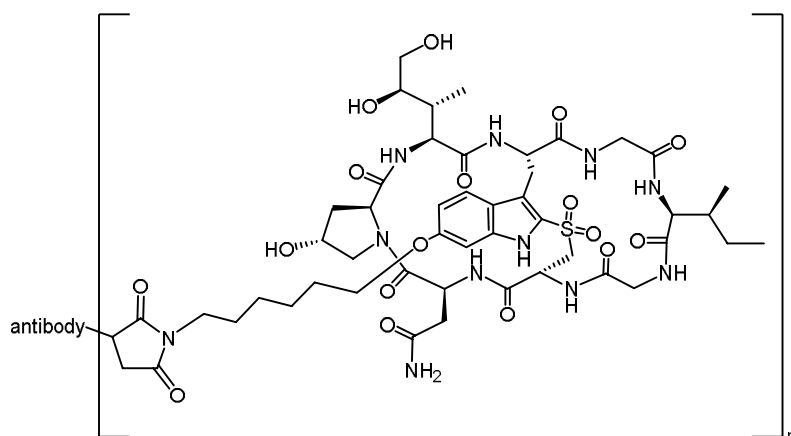
(XVb)







(XXIb)



(XXIIb)

wherein said antatoxin linker moieties are coupled to the thiol groups of cysteine residues of the antibody, and wherein n is preferably from 1 to 10, preferably from 1, 2, 3 to 4, preferably from 1, 2 to 5, preferably from 4 to 7, preferably from 8 to 10.

1516. Use of aA pharmaceutical formulation comprising the composition for use according to any of claims 1 to 1415 in the manufacture of a medicament for the treatment of cancer, further comprising one or more pharmaceutically acceptable buffers, surfactants, diluents, carriers, excipients, fillers, binders, lubricants, glidants, disintegrants, adsorbents, and/or preservatives.

~~1617.~~ The Use of the composition ~~for use~~ according to any of claims 1 to ~~1415~~ in the manufacture of a medicament for the treatment of cancer, or of the pharmaceutical formulation according to claim 1516 in the manufacture of a medicament for the treatment of cancer, wherein said cancer is selected from the group consisting of melanoma, squamous and non-squamous non-small cell lung cancer, metastatic small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, urothelial carcinoma, head and neck squamous cell carcinoma, Merkel cell carcinoma, hepatocellular carcinoma, gastric and gastroesophageal carcinoma, metastatic colorectal cancer, primary mediastinal B cell lymphoma, recurrent or metastatic cervical cancer, and metastatic cutaneous squamous cell carcinoma.

~~18. A method for the treatment of cancer in a human subject in need thereof, wherein the method comprises administering to the subject a composition comprising (a) at least one immune checkpoint inhibitor and (b) at least one conjugate, wherein said conjugate is comprising (i) a target binding moiety, (ii) at least one amatoin, and (iii) optionally at least one linker connecting said target binding moiety with said at least one amatoin.~~

~~19. Use of a composition comprising (a) at least one immune checkpoint inhibitor and (b) at least one conjugate, wherein said conjugate is comprising (i) a target binding moiety, (ii) at least one amatoin, and (iii) optionally at least one linker connecting said target binding moiety with said at least one amatoin, for the treatment of cancer.~~